

PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number (Optional) 890003-2006.1	
I hereby certify that this correspondence is being deposited via EFS-WEB.		Application Number 10/561,826	Filed October 17, 2006
on <u>10/22/10</u>		First Named Inventor Catherine M. Verfaillie	
Signature <u>Mel Rohan</u>		Art Unit 1649	Examiner Chang Yu Wang
Typed or printed name <u>Mel Rohan</u>			
Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.			
This request is being filed with a notice of appeal.			
The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.			
I am the			
<input type="checkbox"/>	applicant/inventor.	<u>Anne Brown</u> Signature	
<input type="checkbox"/>	assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/66)	Anne Brown Typed or printed name	
<input checked="" type="checkbox"/>	attorney or agent of record. Registration number <u>36,463</u>	216-621-2234 Telephone number	
<input type="checkbox"/>	attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____	<u>10/22/10</u> Date	
NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.			
<input checked="" type="checkbox"/>	Total of <u>5</u> forms are submitted		

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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REMARKS

Claims 1, 2, and 5-13 are pending in the present application. Claim 12 has been withdrawn from consideration. Claims 1, 2, 5-9, 11, and 13 remain rejected under 35 U.S.C. § 103 on the grounds that they are unpatentable over Studer (WO 02/086073) in view of Lee (U.S. 2003/0211605). In addition, claims 1-2, 5-11, and 13 are rejected under 35 U.S.C. § 103 on the grounds that they are unpatentable over Studer in view of Lee and further in view of Song (*Methods in Mol. Biol.*, 198:79-88 (2002)). Applicants discuss the primary references, Studer and Lee, only.

The claims are directed to a specific protocol for inducing stem cells to differentiate into neuronal cells. This comprises four sequential steps, each with different factors, and each for seven days. The first step is with basic FGF. The second step is then culturing the cells produced in the first step with FGF8 and SHH. The third step is then culturing the cells produced in the second step with BDNF. The fourth step is then culturing the cells produced in the third step with astrocytes. Each step is performed for at least seven days.

The cited references disclose five discrete protocols for differentiating embryonic stem cells into five different neuronal types. Both of the references teach the same differentiation protocols. WO 02/086073 starts with nuclear transfer embryonic stem cells and U.S. 2003/0211605 starts with blastocyst-derived embryonic stem cells.

The references disclose all of the claimed factors (as well as many others). But for four of the protocols, not all the claimed factors are even used. For one of these protocols (for dopaminergic neurons), SHH, FGF8, and bFGF are used and, optionally, BDNF (among others). But, in this protocol, factors are added out of sequence and/or simultaneously.

In an interview conducted September 8, 2009, Applicants presented a table summarizing the various protocols. In case that this summary will assist in comprehending the references and the various protocols, Applicants attach the summary to this request.

The Examiner's rationale can be found in the paragraph spanning pages 5 and 6 of the Office Action dated October 29, 2009, and is maintained in the first full paragraph on page 4 of the Office Action dated June 22, 2010. The Examiner takes the position that adding the factors sequentially does not produce any superior result because, at the end, the culture contains the same factors and the same ES cells, which would be induced to differentiate into neurons. She takes the position that one would have expected that adding the factors sequentially, and for the duration as claimed, would have been expected to produce the same result as adding the factors together for the shorter duration as shown in the cited references.

To address the Examiner's rationale, Applicants submitted a Declaration from Dr. Catherine Verfaillie, an inventor in the current application, explaining that each factor would have been expected to induce a particular phenotypic effect and that, if factors had been added sequentially rather than simultaneously, it would not have been reasonably predictable that the same phenotype would result. Dr. Verfaillie concludes that, in her opinion, the person of ordinary skill in the art would not have been motivated to alter the referenced procedures as in the claims because they would not have reasonably expected to produce the referenced results.

In the Declaration, Dr. Verfaillie indicates that she has not performed an experimental comparison between the referenced end products and the end products obtained using the claimed method. But she illustrates the principle by way of a differentiation protocol that had been conducted in her laboratory. (Snykers et al., attached to the Declaration). There, adult bone marrow cells were subjected to two protocols (i.e., sequential vs. "cocktail" of factors) to assess the effect on differentiation into hepatocyte-like cells. She explains that sequential exposure to factors in a differentiation protocol can result in quite a different end product than simultaneous exposure (i.e., using a "cocktail" of factors).

The Examiner does not substantively rebut the discussion or evidence submitted in the Declaration. The Examiner summarily dismisses Dr. Verfaillie's Declaration on the grounds that Dr. Verfaillie "fails to provide side-by-side comparisons to demonstrate that the claimed cell types, or end products generated from sequential addition of growth factors, are different from those that are simultaneously exposed to the same growth factors taught in the cited references." See Office Action dated October 29, 2009, page 6. Applicants respectfully submit that this is an erroneous reason to dismiss this Declaration.

Obviousness is premised on what the person of ordinary skill would have been motivated to do and this, in turn, is based on what they would have reasonably expected would successfully produce the result. Accordingly, the opinion of Dr. Verfaillie goes to what the person of ordinary skill in the art would have expected, and not to what actually may have occurred after the fact. A side-by-side comparison, as required by the Examiner, would show what actually occurs. But the proper question is what the person of ordinary skill would have expected to occur.

The Declaration is also dismissed on the grounds that Snykers et al. is irrelevant because the Snykers stem cells are not differentiated into neurons. Applicants respectfully submit that this is also an erroneous reason to dismiss the Declaration without substantive discussion. Dr. Verfaillie presented this evidence to illustrate the general principle that exposure of a stem cell to the same factors, in a different sequence, does not necessarily produce the same result. This, accordingly, was brought in to establish what the person of ordinary skill in the art would have reasonably expected and what they would have been motivated to do based on the knowledge in the art at the time.

In the latest Office Action (dated June 22, 2010), the Examiner has a fairly extended discussion of how *KSR International v. Teleflex* (82 USPQ2d 1385 (2007)) applies. On page 6, the Examiner basically takes the position that sequential as opposed to simultaneous exposure yields predictable results. She deems simultaneous and sequential addition as a "simple substitution" reasonably expected to produce the same results. But this is exactly the erroneous position that the Declaration addresses. And, because the

Examiner (in Applicants' opinion) erroneously dismisses the Declaration, examination can proceed no further except by way of appeal.

For all these reasons, Applicants submit that the rejection should be withdrawn or, at the very least, that the Examiner should issue a new Office Action presenting substantive rebuttal evidence showing that, using the claimed protocol, the person of ordinary skill would have reasonably expected the referenced end product.

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TYPE OF CELL	TEXT
<u>GABA-ERGIC</u> "mitogen" (Not SHH) (Not FGF8)	[0019]
<u>SEROTONERGIC</u> bFGF SHH FGF8	[0016]
<u>ASTROCYTES</u> "mitogen" SHH FGF8	[0017]
<u>OLIGODENDROCYTES</u> "mitogen" SHH FGF8	[0018]
DOPAMINERGIC bFGF SHH FGF8 BDNF (21 suggested)	[0015]